REMARKS

Claim Objections

The Examiner has objected to Claims 1, 2, 4, 17-19, 22-28 and 38 as encompassing more than one invention. Claims 1, 2, 4, 17-19, and 22-28 have been amended to be limited to the elected invention. However, Applicants again expressly reserve the right to petition the final decision on the Restriction Requirement as to Groups I-XI as set forth in the October 23 Office Action, whereby such petition can be, and is, deferred until after final action or upon allowance of the claims. In order to clarify that Applicants are considering the Petition under 37 CFR 1.144 and therefore do not agree that the claims should be limited to the elected embodiment, Claim 38 has not been amended to limit the claims to the elected invention and Claim 39 has been added. Applicants defer cancellation of non-elected inventions until prosecution on the merits has otherwise concluded. Applicants also again expressly reserve the right to pursue the non-elected subject matter one or more divisional applications.

Objection to the Specification and Rejection of Claims 1, 2, 4, 14, 17-19 and 22-23 Under 35 U.S.C. § 112, First Paragraph:

The Examiner has objected to the specification and rejected Claims 1, 2, 4, 14, 17-19 and 22-23 under 35 U.S.C. § 112, first paragraph, on the basis of enablement. Specifically, the Examiner contends that inflammatory cellular infiltration in the airway tissue is an objective measurement of an inflammatory process in the lung, is one of the indications of airway hyperresponsiveness (AHR), and contributes to overall airway hyperresponsiveness. The Examiner then asserts that Applicants' statement that TNF-α could reduce AHR independent of cellular inflammation is inaccurate, if not contradictory, to what is taught in the specification. The Examiner also maintains the position that previous *in vitro* experiments regarding the effect of TNF-α on γδ T cells can not establish predictability of the effect of TNF-α on these cells *in vivo*. The Examiner again asserts that TNF-α is known to have broad and diverse physiological effects *in vivo* and particularly as an immune modulator, and that its effect on AHR is unpredictable. The Examiner refers to three references that allegedly show that TNF-α increased bronchial constriction and airway reactivity. The relevance of the lung inflammation in the TNF-α deficient mice is also emphasized by the Examiner to maintain a position that administration of TNF-α is unpredictable. Finally, the Examiner contends that the terms "practical" and "feasible" are synonyms and that the teaching in U.S. Patent No. 6,429,199 is

relevant to the issue of whether one could administer TNF-α systemically without toxicity and predictably reduce AHR.

Applicants again traverse the rejection of claims under 35 U.S.C. § 112, first paragraph. Initially, the Examiner is respectfully directed to the enclosed Declaration under 37 CFR 1.132, which provides additional experimental data in support of the claims. In particular, the attached Declaration describes experiments in which it is demonstrated that administration of TNF-α *in vivo* reduces airway hyperresponsiveness, that this effect is correlated with γδ T cells, and that the ability of TNF-α to reduce AHR is independent of cellular inflammation in the lungs. These experiments are believed to be sufficient to demonstrate that the present invention operates as claimed and should address many if not all of the Examiner's concerns regarding enablement.

With regard to the issue of inflammation and AHR, Applicants also provide the following additional comments. Applicants do not disagree that many inflammatory diseases of the lung are characterized by airway hyperresponsiveness, among other symptoms, and Applicants also acknowledge that the specification teaches that a "variety of studies have linked the degree, severity and timing of the inflammatory process with the degree of airway hyperresponsiveness." Indeed, the present invention is useful for treating AHR that occurs in a variety of conditions associated with inflammation. However, Applicants disagree that this means that AHR is *solely* linked to inflammation and that only agents that also affect inflammation will affect AHR. AHR is the result of complex pathophysiological changes in the airway (specification, page 2, lines 19-20). Airflow limitation or airway hyperresponsiveness can be caused by collagen deposition, bronchospasm, airway smooth muscle hypertrophy, airway smooth muscle contraction, mucous secretion, cellular deposits, epithelial destruction, alteration to epithelial permeability, alterations to smooth muscle function or sensitivity, abnormalities of the lung parenchyma and infiltrative diseases in and around the airways (specification page 11, line 27 to page 12, line 7). For example, non-adrenergic non-cholinergic (NANC) mechanisms have been described as additional neural pathways that control airway smooth muscle tone in asthma (Barnes, 1996, *J. Allergy Clin. Immunol.* 98:S73-83). While inflammation can be associated with many of these causes, it is incorrect to then state that every agent that reduces AHR acts via modulation of the inflammatory response, since an agent may act directly on a specific mechanism that induces AHR or act on a cell or protein that then influences AHR. In the present invention, the inventors have provided extensive evidence that the effects of TNF-α are correlated with γδ T cells, which may, for example, regulate or affect the activity of other

cells (e.g., airway smooth muscle cells) and be unrelated to any inflammation which may contribute to the disease state of the patient. Therefore, Applicants' point is that, even though AHR or a predisposition therefor may be associated with an inflammatory condition, it is certainly conceivable that a given agent can operate to reduce AHR by a mechanism that is independent of having an effect on or being influenced by cellular inflammation. Indeed, as stated in the specification, the present inventors' data indicates that the usefulness of modulating γδ T cell activity in regulating AHR does not appear to be restricted to AHR in the context of inflammation (e.g., Example 4, last sentence).

As discussed in the last response, the independence of the cellular inflammation associated with TNF-α and γδ T cells does not render the invention unpredictable, but rather illustrates another novel finding by the inventors (i.e., while γδ T cells clearly play a role in the regulation of airway tone following airway exposure to allergen (e.g., by influencing cells such as alveolar macrophages, airway epithelial cells and airway smooth muscle cells), this effect is independent of the inflammatory cellular response). The data provided in the Declaration under 37 CFR § 1.132 confirms and further demonstrates this point.

With regard to the Examiner's position regarding the effect of TNF-α in *in vitro* experiments, the Declaration provides a direct demonstration that the administration of TNF-α reduces AHR *in vivo* in an art-accepted model of airway hyperresponsiveness. Moreover, the experiments in the Declaration demonstrate that the effect of TNF-α is associated with γδ T cells, providing further evidence that the invention operates as disclosed in the specification.

With regard to the references cited by the Examiner, Applicants have the following comments. First, in Wheeler et al., human recombinant TNF-α was administered intravenously to sheep and the sheep were challenged by administration of nebulized histamine to induce airway hyperresponsiveness. TNF-α increased the airway hyperresponsiveness to the histamine challenge. However, as previously discussed, the murine model of airway hyperresponsiveness used in the present experiments has been shown prior to the present invention to be an art-accepted model of airway hyperresponsiveness and allergic inflammation, which shares many characteristics with human respiratory conditions and particularly with allergic inflammation. This murine model has been published extensively and the phenotype is not limited to the genetic background of the C57Bl/6 mouse (For example, Renz et al., 1992, *J. Allergy Clin. Immunol.* 89:1127-1138; Larsen et al., 1992, *J. Clin. Invest.* 89:747-752; and Saloga et al., 1993, *J. Clin. Invest.* 91:133-141). Moreover, the murine model is useful *not only* for studying the effects of inflammation on allergic

responses, but also for studying the basic mechanisms of airway hyperresponsiveness, which as discussed above, includes events that occur downstream of or in addition to the inflammatory process. The present inventors have shown that the present invention operates in the manner as claimed using this art-accepted model.

In Wagner, TNF-α was perfused into the pulmonary vascular of sheep and was shown to cause bronchial vascular constriction. However, the sheep were not undergoing or predisposed to undergo airway hyperresponsiveness prior to administration of the TNF-α, and Wagner did not measure airway smooth muscle reactivity (see page H950, column 1, first full paragraph). Moreover, Wagner states on page H948, column 1, first partial paragraph, that "[n]either index of airway smooth muscle tone was altered by TNF-α infusion". Furthermore, at page H950, column 1, first full paragraph, while Wagner supposes that the vascular constriction *might* contribute to the airways hyperresponsiveness observed by Wheeler et al., she acknowledges that no bronchoconstriction occurred in the smooth muscle cells in their studies. Therefore, it is not believed that Wagner provide a sufficient disclosure to discount the findings of the present invention, particularly since that study did not measure airway hyperresponsiveness.

Martin et al. studied the effects of both IL-1β and TNF-α on isolated rat lungs (i.e., *in vitro*) and the authors note at page L599, col. 1, end of full paragraph, that "the caveat should be made that under in vivo conditions, factors such as blood and a functioning nerve supply might modify responses". Finally, given that Martin et al. is performed on isolated rat lungs, the effects of γδ T cells *in vivo* to which the present invention is directed, can not be accurately assessed or accounted for. Therefore, Martin et al. can not be considered prejudicial to the results provided by the present invention.

With regard to Claims 30 and 31, Applicants again submit that the teachings of the prior art are rebutted by the data and arguments presented herein, and it is again submitted that the parameters in Claims 30 and 31 are representative of one measure of therapeutic benefit that can be achieved by the method of the invention.

With regard to the issue of route of administration, Applicants have limited the claims to the administration of TNF-α to the lung of the mammal. As set forth in the specification, administration to the lung can be achieved, for example, by inhaled, intratracheal and nasal routes. These routes of administration are well known in the art and such routes are exemplified in the specification and demonstrated for TNF-α in the Declaration. As for the toxicity of TNF-α, the enclosed Declaration

alone clearly shows that TNF-α can be administered in a therapeutically effective amount without being toxic or lethal to the animal.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 2, 4, 14, 17-19 and 22-23 under 35 U.S.C. § 112, first paragraph.

Rejection of Claims 1, 24, 29-31, 36 and 38 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has rejected Claims 1, 24, 29-31, 36 and 38 under 35 U.S.C. § 112, second paragraph.

First, the Examiner asserts that Claims 1, 36 and 38 are incomplete for failing to have a positive step or recitation that relates back to the preamble. Applicants have amended the independent claim to positively recite that administration of TNF-α reduces airway hyperresponsiveness in the mammal.

Second, the Examiner objects to Claim 24 for the recitation of "said animal." Applicants have amended Claim 24 to correct this clerical error and recite "said mammal."

Third, the Examiner contends that there is insufficient antecedent basis for the limitation "said step" in Claims 29, 30, and 31. Applicants have amended these claims to clarify the antecedent basis.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 24, 29-31, 36 and 38 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1, 2, 4, 14, 17-19, 22, 25, 36 and 37 Under 35 U.S.C. § 102(b):

The Examiner has rejected Claims 1, 2, 4, 14, 17-19, 22, 25, 36 and 37 under 35 U.S.C. § 102(b), contending that these claims are anticipated by Wheeler et al. Specifically, the Examiner contends that Wheeler et al. teach a method comprising intravenous administration of TNF-α in a pharmaceutically acceptable excipient to the lung of a mammal which the Examiner alleges would inherently activate γδ T cells in the lung. The Examiner notes that the phrase "to reduce airway hyperresponsiveness" has not been given patentable weight because the phrase is in the preamble.

Applicants have amended Claims 1, 2, 4, 14, 17-19, 22, 25, 36 and 37 under 35 U.S.C. § 102(b) to positively recite in the body of the claim that administration of TNF-α reduces airway

hyperresponsiveness in the mammal. Wheeler et al. do not teach or suggest the administration of TNF-α to reduce AHR in a mammal and therefore, Wheeler et al. do not teach or suggest the claimed invention.

In view of the foregoing amendments and remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1, 2, 4, 14, 17-19, 22, 25, 36 and 37 under 35 U.S.C. § 102(b).

Applicants have attempted to respond to all of the issues as set forth in the April 11 Office Action and submit that the claims are in a condition for allowance. In the event that the Examiner has any further questions or comments regarding Applicants' position, the Examiner is requested to contact the below-named agent in an effort to expedite prosecution.

Respectfully submitted,

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Date: October 13, 2003

U.S. Application Serial N . 09/672,865

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re the Application of:

GELFAND et al.

Serial No.: 09/672,865

Filed: September 28, 2000

Atty. File No.: 2879-68

For: "REGULATION OF γδ T CELLS TO REGULATE AIRWAY HYPERRESPONSIVENESS"

Group Art Unit: 1632

Examiner: Li, Quan J.

DECLARATION OF ERWIN W. GELFAND (Under 37 CFR 1.132)

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

I, Erwin W. Gelfand, declare as follows:

1. I am a co-inventor of the above-referenced patent application and am familiar with the application. I am a skilled artisan in the fields of immunology and disorders of the airways.

2. This Declaration is being submitted in conjunction with an Amendment and Response to an Office Action having a mailing date of April 11, 2003.

3. The following discussion is provided in response to the Examiner's rejection of Claims 1, 2, 4, 14, 17-19, 22-33, and 36-38 under 35 U.S.C. § 112, first paragraph. Specifically, the following discussion and attached figures demonstrate that administration of tumor necrosis factor-α (TNF-α) inhibits airway hyperresponsiveness in sensitized and challenged mice, and that this effect is mediated via an effect on the activity of γδ T cells. The data also show that administration of TNF-α reduces airway hyperresponsiveness independently of cellular inflammation in the lung.

More specifically, Figure A shows the study protocol for the experiments described herein. Briefly, using the protocols as described in the Examples of the above-identified application for the experimental model of airway hyperresponsiveness, mice were sensitized and challenged with ovalbumin, and airway responsiveness was assessed as a change in airway function after challenge with aerosolized methacholine (MCh). Also as described in the present application, maximum values

of R_L, and minimum values of C were used to express changes in murine airway function. Three groups of mice were depleted of γδ T cells by administration of monoclonal antibody against TCR-δ as described in the application at days 24 and 25 after the initial sensitization to ovalbumin. Two of the groups of γδ-depleted mice, and two groups of mice with intact γδ T cells were administered either 5ng or 500ng of TNF-α, or with PBS as a control, intranasally before the first nebulized ovalbumin challenge at day 28 and between the second and third ovalbumin challenges at days 29 and 30. 48 hours later, determination of airway responsiveness and inflammation was assessed using aerosolized methacholine (MCh) and examination of BAL fluid, respectively, as described in detail in the application.

Figure B shows that administration of 500 ng of TNF-α reduced airway hyperresponsiveness as compared to controls in both the larger airways, as assessed by airway resistance (R_L) and the smaller airways, as demonstrated by changes in dynamic lung compliance. In mice lacking γδ T cells, the effect of TNF-α was abolished, indicating that the effect of the TNF-α treatment relies on the presence of γδ T cells, as already set forth in the above-identified application.

Figure C shows the BAL fluid cell composition for total cells, macrophages, lymphocytes, neutrophils and eosinophils. These results show that inflammation as measured by the numbers of cells in the BAL fluid did not significantly change with treatment. Therefore, the effect of the TNF-α treatment is not associated with inflammation in the lung.

Therefore, these data show that administration of TNF-α reduces airway hyperresponsiveness, that this effect is associated with γδ T cells, and that the effect is not associated with inflammation.

4. I hereby declare that all statements made herein of my own are true and that all statements made on information and belief are believed to be true; and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

Date: 10.10.03

By: _____
Erwin W. Gelfand